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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: CORE-CENTERED GRANULE COMPOSED OF MICRO-STRUCTURE BODY

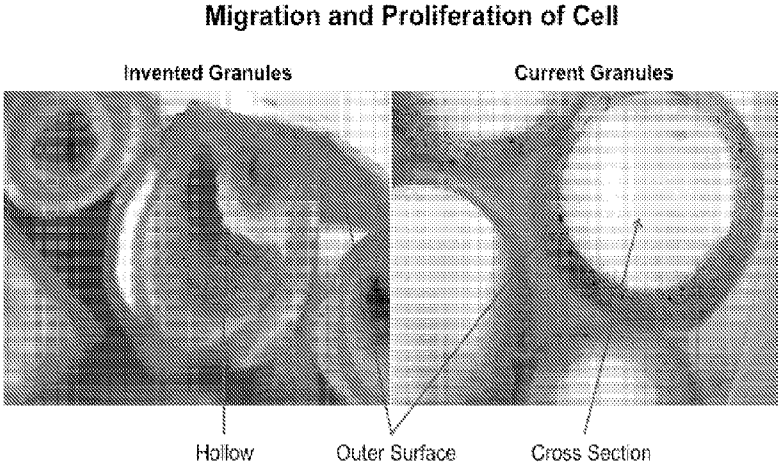


Fig. 3

(57) **Abstract**: Granules useful for bone regenerative filler that exhibit enhanced cell migration and proliferation and differentiation.

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CORE-CENTERED GRANULE COMPOSED OF MICRO-STRUCTURE BODY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/909,037 filed November 26, 2013, the contents of which are hereby incorporated by reference in their entirety.

Field of the Disclosed Subject Matter

[0002] The disclosed subject matter is a granule that facilitates cell migration and proliferation and differentiation. The granule has a generally tubular body having an outer surface and at least one inner surface defining one or more cores. A matrix is disposed between the outer surface of the granule and at least one inner surface. Pluralities of granules constitute bone regeneration filler. The granules may be used for orthopedic or dental and craniomaxillofacial applications.

Background

[0003] Conventional granules used for bone regenerative filler have solid spherical bodies. One drawback of the solid spherical bodies is low population of cell attachment and proliferation as well as a higher fraction of surgical site was occupied by material than core-centered granule, less space for cell ultimately bone regeneration. It has been unexpectedly found that granules having a generally tubular structure with at least one core defined in the body facilitates cell migration and/or proliferation rate.

SUMMARY

[0004] In accordance with one aspect of the subject matter, a granule that facilitates cell migration and/or proliferation is provided. The granule has a hollow, tubular body. The tubular

body is defined by an outer surface and an inner surface separated by a matrix. The matrix extends between the outer and inner surfaces of the tubular body. The matrix composed of porous micro-structure to facilitate the absorption of natural bone repair-promoting factors in extracellular fluids result in enhancing bone regeneration. The tubular body further includes at least one core which defines an opening extending throughout the tubular body. The core and porous micro-structure permits fluid flow into and out of the tubular body and facilitates cell migration and proliferation within the granule by providing large surface area than solid granule. The micro-structure can be less than 5 micron, or about 10 micron to about 50 micron. The inner core can be less than 150 micron, or about 200 micron to about 500 micron. The granule can be less than 500 micron, or about 1 mm to about 3 mm in length and about 700 micron to about 1500 micron in diameter depending on application.

[0005] In one embodiment, the outer surface of the granule is porous. The porous nature of the outer surface permits fluid flow into and out of the granule. The inner surface of the granule defines the outer contours of a core. The defined core extends through the granule body defining the generally tubular structure. The at least one core may be disposed in the center of the granule body or off-center. In some instances, multiple cores are defined in the granule body. For example, in one embodiment, three cores defining three openings through the tubular body exist. The core permits cell migration into the granule.

[0006] A matrix interconnects the core and is disposed between the inner and outer surface of the granule body.

[0007] In some embodiments, the granule is loaded with beneficial agent. The beneficial agent for example can be a drug including antibacterial or a bio-molecular agent including bone morphogenetic protein or transforming growth factor beta. In one embodiment, the beneficial agent

is loaded into the granule by way of biodegradable microspheres. The microspheres may be, for example, disposed in the matrix or attached to the inner or outer surface of the tubular body. In another embodiment, the beneficial agents include an anti-inflammatory agent or a bone growth factor.

[0008] In another aspect, a process of fabricating hollow tubular granules, the process comprises: mixing HA powder and water until HA transforms into hollow filaments, subjecting the HA filaments to freezing, and heating the filaments. The mixing step includes stirring the HA until it forms a paste. The freezing step includes subjecting the filaments to liquid nitrogen. The heating step includes a first heating step and a second heating step. The first heating step includes subjecting the filaments to a temperature of about 600°C for a period of time. The period of time is about one hour. The second heating step includes subjecting the filaments to a temperature of about 1230°C for a period of time. The period of time is about three hours.

[0009] In another aspect, the bone regenerative filler comprising: a plurality of granules, wherein each of the plurality of granules includes a hollow tubular body having an outer surface and an inner surface separated by a matrix, and at least one core defining an opening extending through the tubular body, wherein the outer surface is adapted to permit fluid flow into and out of the matrix. The plurality of granules permits cell migration and proliferation and differentiation. The granules facilitate cell proliferation and differentiation over a period of time. For example, the bone regenerative filler can facilitate migration or proliferation of more than 2×10^5 cells in less than one week.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] A detailed description of various aspects, features, and embodiments of the subject matter described herein is provided with reference to the accompanying drawings, which are briefly described below. The drawings are illustrative and are not necessarily drawn to scale, with some components and features being exaggerated for clarity. The drawings illustrate various aspects and features of the present subject matter and may illustrate one or more embodiment(s) or example(s) of the present subject matter in whole or in part.

[0010] **FIG. 1A to 1D** are SEM images of granules in accordance with the disclosed subject matter.

[0011] **FIG. 2** shows SEM images of the outer surface and porous micro-structure matrix of the granules shown in FIG. 1. FIG. 2C shows the availability of drug or beneficial biologic reagent delivery by biodegradable microspheres.

[0012] **FIG. 3** shows images of the granules of FIG. 1 and granules of the prior art depicting that the granules of FIG. 1 facilitate greater cell migration and exhibit better cell attachment than granules of the prior art.

[0013] **FIG. 4** depicts a comparative MTT assay of the granules in accordance with the disclosed subject matter and the granules of the prior art showing that the granules of the subject application exhibit higher cell proliferation.

[0014] **FIG. 5A** illustrates a plurality of granules loaded with beneficial agents.

[0015] **FIG. 5B** illustrates an expected release kinetics of the granules of **FIG. 5A**.

[0016] **FIG. 6** shows greater new bone formation with invented granules than current granules.

[0017] **FIG. 7** depicts a comparative bone volume of the granules in accordance with the disclosed subject matter and the granules of the prior art showing that the granules of the subject application exhibit higher new bone formation.

[0018] **FIG. 8** illustrates various applications of the bone regenerative filler in accordance with the disclosed subject matter.

[0019] **FIG. 9** is a schematic diagram of an exemplary method of making the granule in accordance with the disclosed subject matter.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Core-Centered and Porous Ceramic Granule

[0020] In one embodiment, macro- (150-500 um) and micro – (5-50 um) structural porous ceramic granules loaded with a beneficial agent are provided. The granule can provide a drug delivery system by using biodegradable polymeric spheres. For example, the granule may be suitable for bone regeneration after damage caused by injury or disease.

[0021] As depicted in FIGS. 1A to 1D, a granule 10 having a core-centered structure is depicted. Referring to FIG. 1B, the granule 10 has an outer surface 100, and inner surface 120 and a matrix 300 defined between the inner 120 and outer 100 surfaces. A core 200 is disposed in the granule body and the outer contour of the core 200 is defined by the inner surface 120 of the granule. In one embodiment, as shown in FIGS. 1C and 1D, the granule includes more than one inner surface 130, 140, and 150 defining multiple cores 210, 220, 230.

[0022] The core-centered structure provides a larger surface area for facilitation of cell attachment. The micro-structure 310 in the body and micro pores 110 on its outer surface promote fluid flow, such as nutrients and/or natural bone repair-promoting factors but not limited, in and out

of the granule. Localized beneficial agents, such as drug or growth factors, can be loaded within the granule. Thus, as shown in FIG. 2, the granule can provide a delivery system using, for example, biodegradable polymeric microspheres 400 loaded with beneficial agent. Various beneficial agents can be used such as anti-inflammatory agents and bone growth factors but not limited.

[0023] In another aspect, a method of making the granules is provided. As shown in FIG. 7, one exemplary method for making the granules includes using a water based ceramic slurry coating on fiber filament (thread, twine, yarn, etc.) followed by a freeze-dry method. The ceramic slurry was prepared using hydroxyapatite/solution at a ratio of 0.6-0.7. Binders (3% high molecular weight polyvinyl alcohol, 3% carboxymethylcellulose, and 5% ammonium polyacrylate dispersant) were added to the slurry mixture to improve sintering and the stability of the core-centered granule structure. The filament was coated by prepared HA slurry, then frozen in liquid nitrogen. After complete freeze, it was coated again with HA slurry to freeze in the liquid nitrogen. These steps were repeated until the granule wall attained the desired thickness. The granules were lyophilized using a freeze-dryer overnight. During the lyophilization, the frozen water molecules sublimated and created micro-structures in the body of the granule. Heating followed at 1230°C for 5 hours by increasing the temperature at a rate of 5°C/min. Then, the furnace was cooled permitting the sintered granules inside to come back down to room temperature at a cooling rate of 5°C/min. During the heat treatment, the filament material dissipated leaving an open core in the granule.

Polymeric Microspheres for Beneficial Agent Delivery

[0024] In some embodiments, the granule is loaded with beneficial agent. For example, the beneficial agent can be loaded in microspheres for attachment to the granule body. The non-porous

or porous polymeric microspheres for beneficial agent delivery can be fabricated using water/oil (double emersion) or water/oil/water (triple emersion) methods. The polymeric microspheres can be immobilized onto the granule surface and/or inside the micro-structure using electro static techniques. The biodegradable polymeric microspheres can be used as delivery system for antibiotics and/or protein and/or growth factor, etc. After loading the beneficial agent, e.g., the antibiotics and/or protein and/or growth factor, the polymeric microspheres will be attached onto the granules by surface modification by oxygen plasma treatment and/or positive or negative coating method. In this case, after implantation of the granules into a subject, the beneficial agent, e.g., antibiotics, will be released during a first time period e.g., in one week to prevent severe infection of the surgical site. In the second stage protein and/or growth factor or other beneficial agents will be gradually released for up to four weeks to accelerate bone regeneration (Fig 5B).

[0025] For example but without limitation, the granules can be made by hydroxyapatite (HA), tri-calcium phosphate (TCP), HA/TCP composite, any other calcium phosphate family, bio glass, alumina, zirconia, and titanium dioxide, etc. The polymeric microspheres can be made by Polyglycolide (PGA), Poly-L-lactide (PLLA), poly(lactic-co-glycolic acid) (PLGA), Poly-ε-caprolactone (PCL), Poly-D, L-lactide (PDLLA), Poly-1,4-dioxane-2-one (PDO), Polytrimethylenecarbonate (PTMC), and Poly-β-hydroxybutyrate (PHB), etc.

[0026] The granules can be used directly as a bone substitute without a beneficial agent delivery system. However, the combined system with polymeric microspheres may be useful for bone tumor treatment or periodontal disease treatment.

Cellular Reponses for Hollow and Porous HA Granules

[0027] Proliferation rate was higher on invented granules than current granules during the observed period of time. Cell attachment was clearly evidenced for both types of granule. However, the invented granule has a hollow structure in the granule body, enhancing cell migration. Based on these findings, the granules disclosed herein can be employed for treatment of bony defects caused either by trauma or massive disease surgeries.

[0028] In addition the disclosed subject matter is also directed to other embodiments having any other possible combination of the dependent features claimed below and those disclosed above. As such, the particular features presented in the dependent claims and disclosed above can be combined with each other in other manners within the scope of the disclosed subject matter such that the disclosed subject matter should be recognized as also specifically directed to other embodiments having any other possible combinations. Thus, the foregoing description of specific embodiments of the disclosed subject matter has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the disclosed subject matter to those embodiments disclosed.

CLAIMS

1. A granule comprising:

a tubular body having an outer surface and an inner surface separated by a matrix, and

at least one core defining an opening extending through the tubular body, wherein the outer surface is adapted to permit fluid flow into and out of the matrix.

2. The granule of claim 1, wherein the outer surface is porous.

3. The granule of claim 1, wherein the inner core is about 200 micron to about 500 micron.

4. The granule of claim 1, wherein the porous micro-structure is about 10 micron to about 50 micron.

5. The granule of claim 1, wherein the granule is about 1 mm to about 3 mm in length.

6. The granule of claim 1, wherein the granule is about 700 micron to about 1500 micron in diameter.

7. The granule of claim 1, wherein the at least one core is disposed in the middle of the tubular body.

8. The granule of claim 1, wherein the at least one core includes three cores defining three openings through the tubular body.

9. The granule of claim 6, wherein the matrix interconnects the three cores.

10. The granule of claim 1, wherein the core permits cell migration into the core.

11. The granule of claim 1, wherein the granule includes first, second, and third cores.

12. The granule of claim 1, wherein the granule further is loaded with a beneficial agent.

13. The granule of claim 10, wherein the beneficial agent is loaded into one or more microspheres disposed in the granule.

14. The granule of claim 11, wherein the microspheres are disposed in the matrix.

15. The granule of claim 11, wherein the microspheres are attached to the inner or outer surface or porous micro-structure of the tubular body.

16. The granule of claim 10, wherein the at least one beneficial agent is an anti-inflammatory agent or a growth factor.

17. A process of fabricating hollow tubular granules, the process comprising:

mixing HA powder and water until HA transforms into hollow filaments,

subjecting the HA filaments to freezing, and

heating the filaments.

18. The process of claim 15, wherein the mixing step includes stirring the HA until it forms a paste.

19. The process of claim 15, wherein the freezing step includes subjecting the filaments to liquid nitrogen.

20. The process of claim 15, wherein the heating step includes a first heating step and a second heating step.

21. The process of claim 18, wherein the first heating step includes subjecting the filaments to a temperature of about 600°C for a period of time.

22. The process of claim 19, wherein the period of time is about one hour.

23. The process of claim 18, wherein the second heating step includes subjecting the filaments to a temperature of about 1230°C for a period of time.

24. The process of claim 21, wherein the period of time is about three hours.

25. Bone regenerative filler comprising:

a plurality of granules, wherein each of the plurality of granules includes a hollow tubular body having an outer surface and an inner surface separated by a matrix, and

at least one core defining an opening extending through the tubular body, wherein the outer surface is adapted to permit fluid flow into and out of the matrix.

26. The bone regenerative filler of claim 23, wherein the plurality of granules permits cell migration and proliferation.

27. The bone regenerative filler of claim 24, wherein the granules facilitate cell proliferation and defferntiation over a period of time.

28. The bone regenerative filler of claim 25, wherein more than 2 x 10^5 cells migrate or proliferate in less than one week.

29. The bone regenerative filler of claim 25, wherein about 3 x 10^5 cells migrate or proliferate in the granule in about one week.

30. The bone regenerative filler of claim 25, wherein about 22% new bone formation in the granules in 4 weeks after implantation.

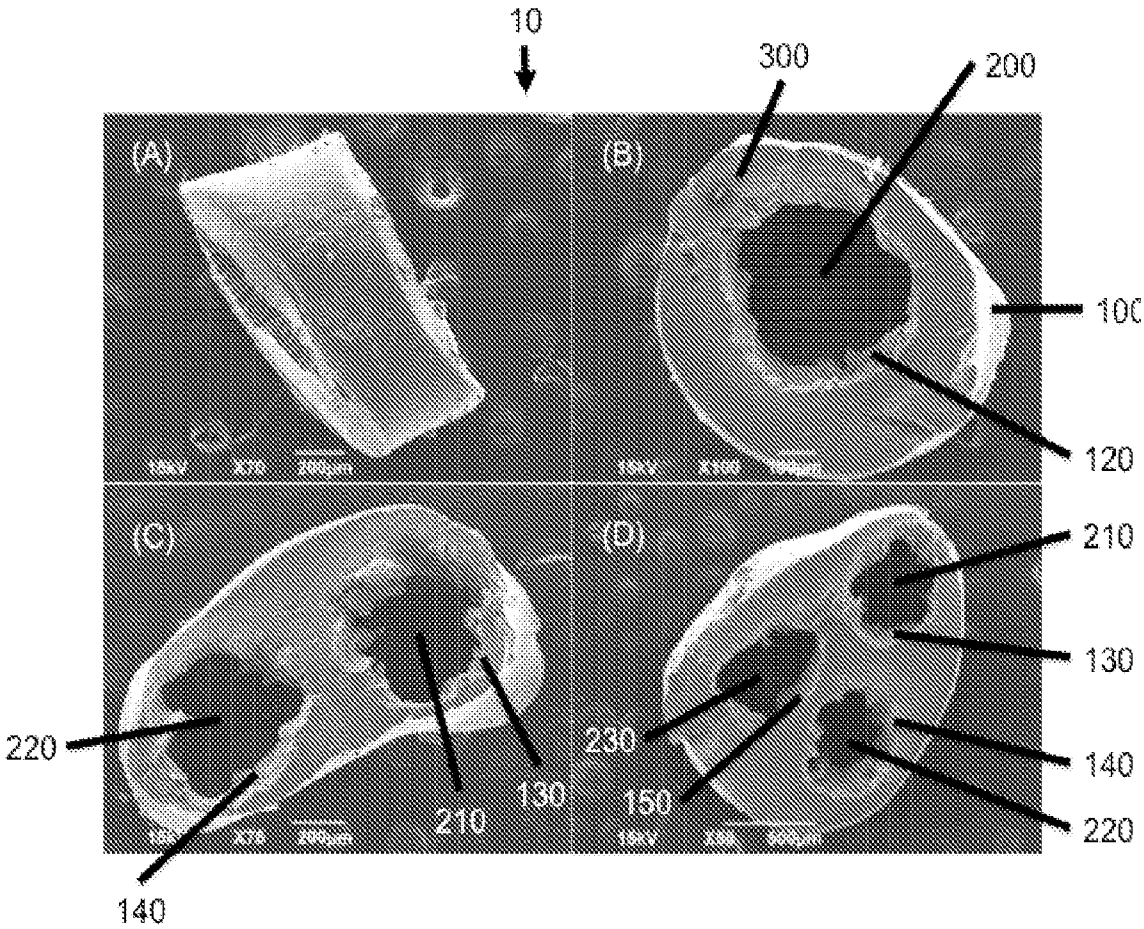


Fig. 1A to 1D

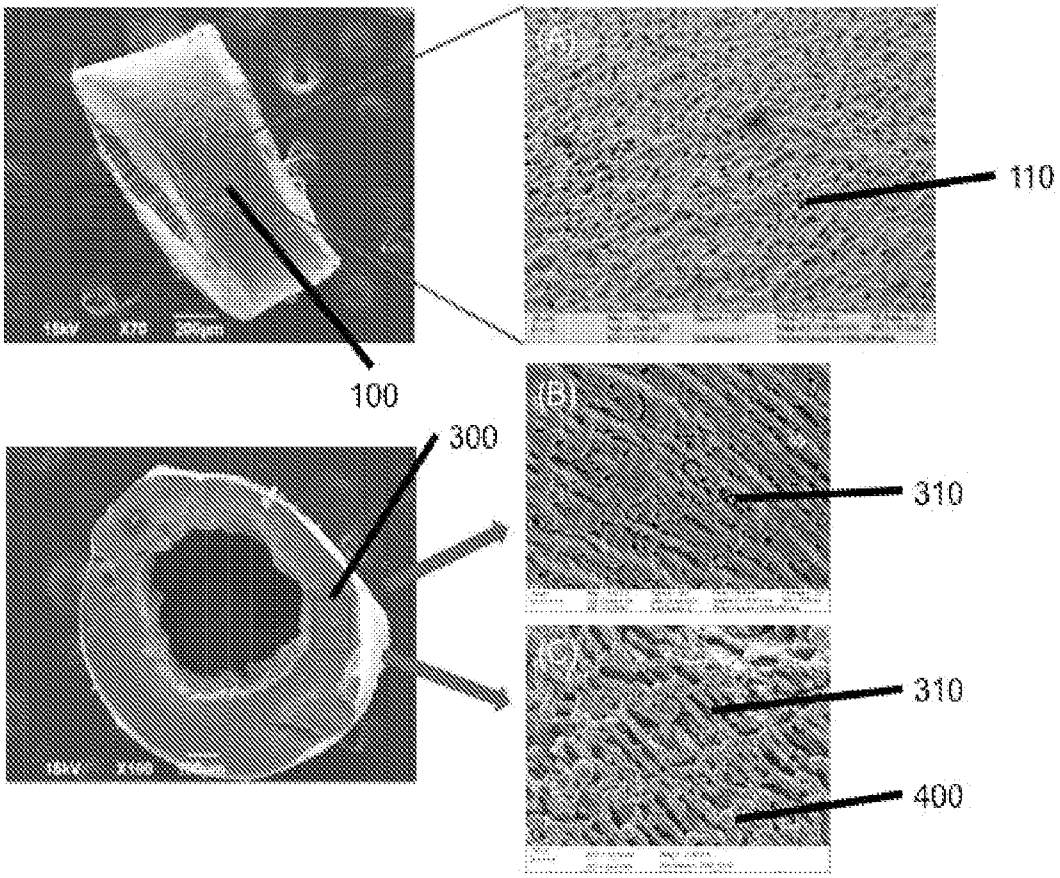


Fig. 2

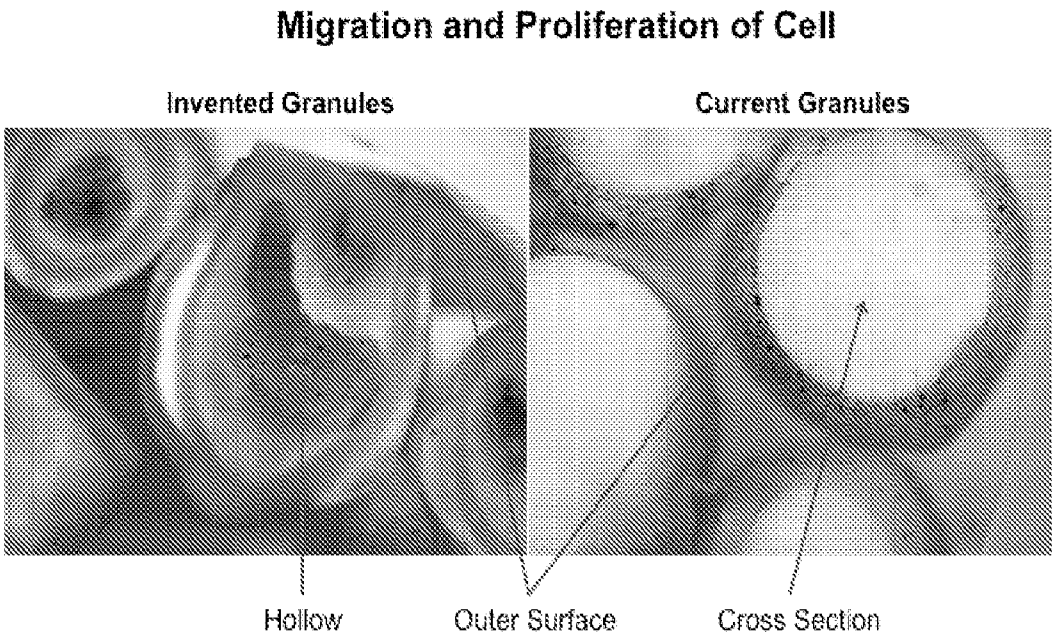

Migration and Proliferation of Cell
Invented Granules
Current Granules
Hollow
Outer Surface
Cross Section

Fig. 3

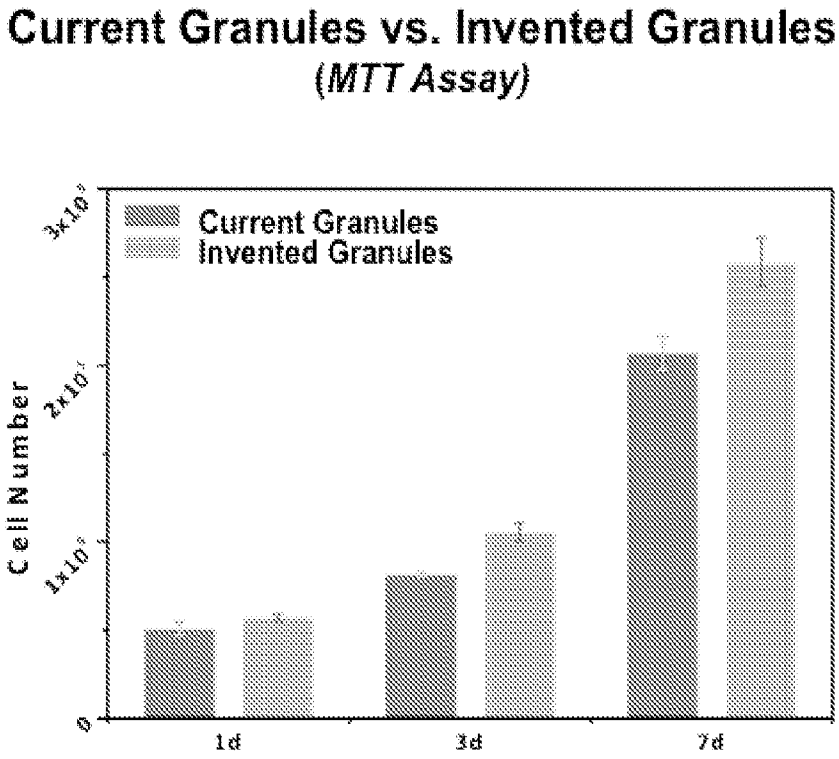

Current Granules vs. Invented Granules
(MTT Assay)
Current Granules
Invented Granules
Cell Number
3x10
2x10
1x10
0
1d
3d
7d

Fig. 4

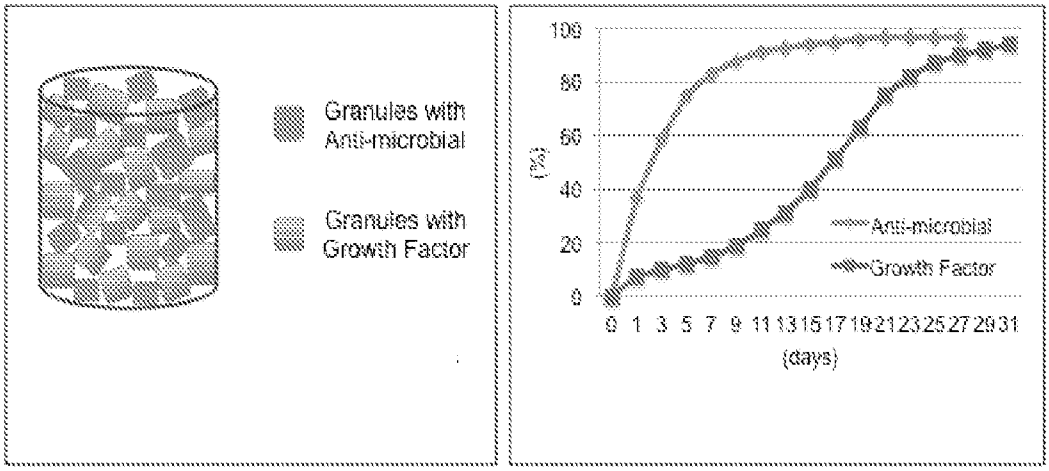


Figure 5A and 5B

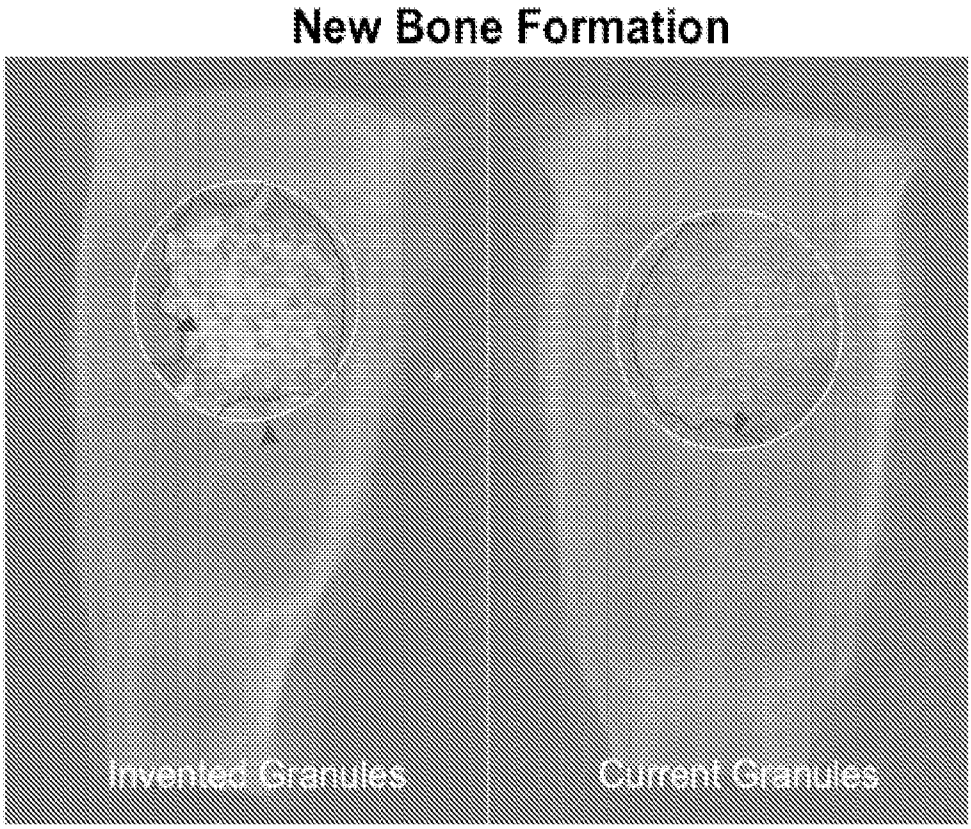


Fig. 6

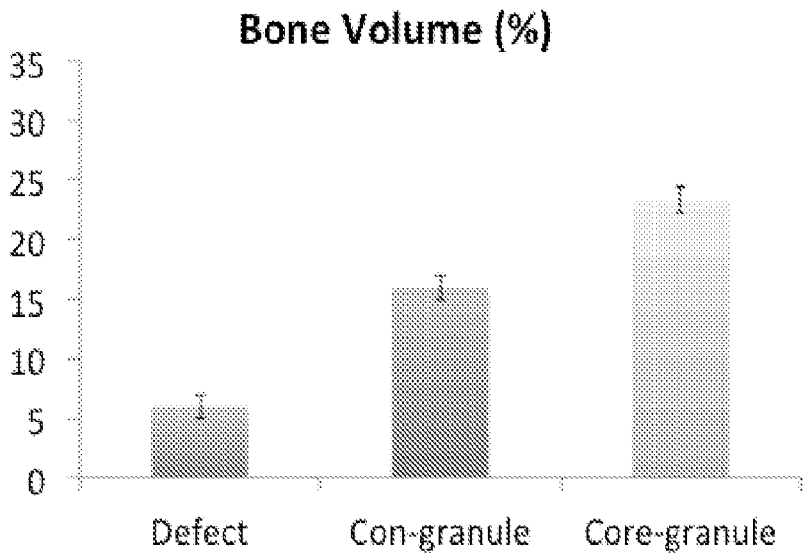

Bone Volume (%)
35
30
25
20
15
10
5
0
Defect
Con-granule
Core-granule

Fig. 7

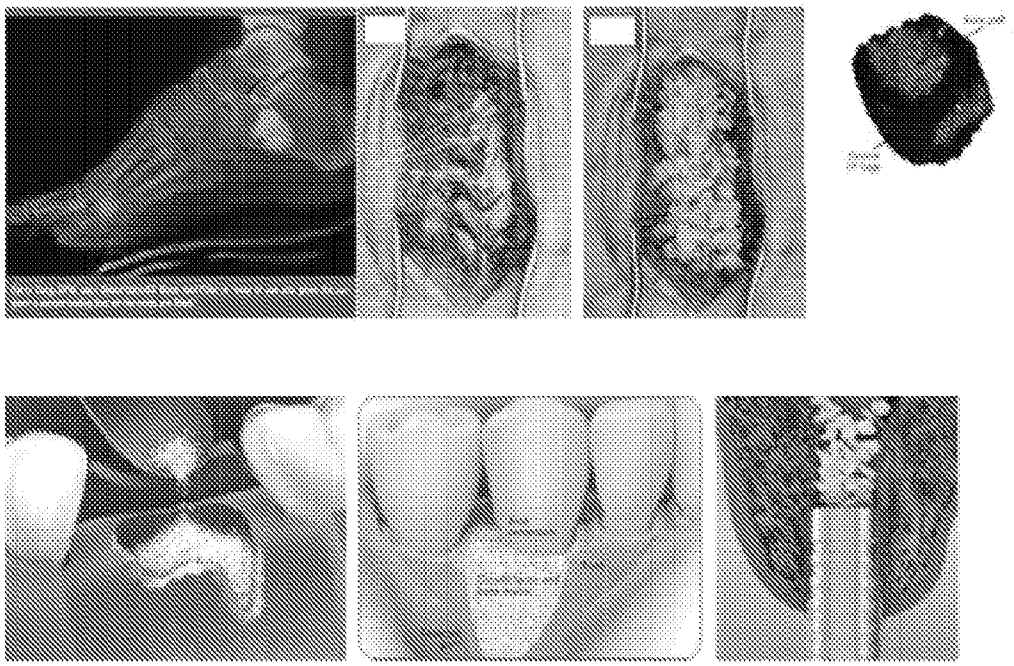


Fig. 8

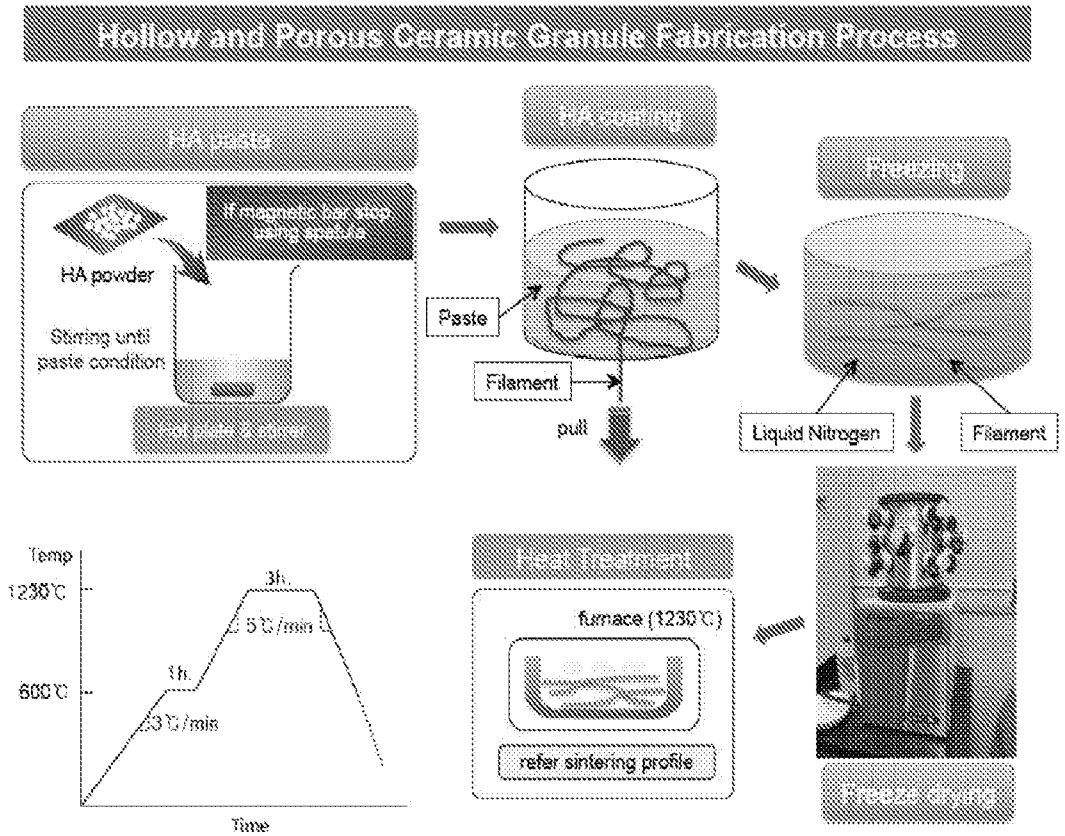

Hollow and Porous Ceramic Granule Fabrication Process
HA powder
Stirring until paste condition
Paste
Filament
pull
Liquid Nitrogen
Filament
furnace (1230℃)
refer sintering profile
Temp
1230℃
600℃
1h
3h
5℃/min
3℃/min
Time

Fig. 9

INTERNATIONAL SEARCH REPORT

~~14/067375 02.04.2015~~

International application No.
PCT/US 14/67375

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61F 2/08, 2/28, 2/30; A61L 27/40, 27/56 (2015.01)
CPC - A61L 27/56; A61F 2002/2835

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61F 2/08, 2/28, 2/30; A61L 27/40, 27/56 (2015.01)
CPC - A61L 27/56; A61F 2002/2835

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61F 2/28, 2/2846, 2/30, 2002/30766, 2230/0069, 2240/001, 2250/0023, 2250/0024, 2250/0051, 2250/0052; A61L 27/00, 27/40, 2430/00, 2430/02, 2430/06, 2430/12

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase; Google Patents; Google Scholar; Google Web; Espacenet; Search Terms: aqeuous, bone*, cells*, core*, cylind*, day*, diameter*, filament*, filler*, freez*, granule*, HA, heat*, hollow*, hydroxyapatit*, length*, liquid*, matrix*, micrometer*, micron*, mm, nitrogen*, oss*, paste*, pore*, poros*, porous*, proliferat*, scaffold*, shell*, sinter*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0313538 A1 (Oh et al.) 22 December 2011 (22.12.2011), Figs. 1A-1B, para [0051]	1-4, 6-7, 10, 12-18 and 20-30 ---------- 5, 8-9, 11 and 19
Y	US 5,650,108 A (Nies et al.) 22 July 1997 (22.07.1997), col. 6, ln. 58-59	5
Y	US 2008/0281355 A1 (Mayer et al.) 13 November 2008 (13.11.2008), Fig. 15, para [0090]	8-9 and 11
Y	US 2002/0006427 A1 (Umezu et al.) 17 January 2002 (17.01.2002), para [0048]	19
A	US 2004/0034434 A1 (Evans et al.) 19 February 2004 (19.02.2004), para [0136]	1-30
A	US 2006/0292198 A1 (Dalal et al.) 28 December 2006 (28.12.2006), para [0058], [0080]-[0081]	1-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2015 (13.03.2015)	02 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

14/067375 02.04.2015

International application No.
PCT/US 14/67375

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--- See supplemental box ---

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continuation of Box No. III - Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-16 and 25-30, directed to a granule and bone regenerative filler using granules.

Group II: Claims 17-24, directed to a process of fabricating tubular granules.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features

Group I includes the special technical features of a granule, wherein the granule includes a hollow tubular body having an outer surface and an inner surface separated by a matrix, and at least one core defining an opening extending through the tubular body, wherein the outer surface is adapted to permit fluid flow into and out of the matrix that are not required by Group II.

Group II includes the special technical features of mixing HA powder and water until HA transforms into hollow filaments, subjecting the HA filaments to freezing, and heating the filaments that are not required by Group I.

Common Technical Features

Groups I and II share the technical feature of a tubular body / hollow filament. However, this shared technical feature does not represent a contribution over the prior art as being anticipated by US 2011/0313538 A1 to Oh et al. (hereinafter 'Oh') which discloses a tubular body / hollow filament (1, Figs. A-B; para [0051]).

Therefore, Groups I and II lack unity under PCT Rule 13.

**NOTE - Claims 18, 19 and 20 depend from claim 15. However, claims 18, 19 and 20 are process claims and claim 15 is a claim for a granule. For purposes of this opinion, claims 18, 19 and 20 are treated as depending from claim 17.